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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/753,078	01/08/2004	David H. Reifsnyder	12441.00050/16331.004	6550

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EXAMINER	
SCHNIZER, HOLLY G	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 02/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/753,078	REIFSNYDER ET AL.	
	Examiner	Art Unit	
	Holly Schnizer	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *20-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/10/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-19 in the reply filed on 11/14/05 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Therefore, the restriction requirement is deemed proper and is made FINAL.

Status of the Claims

Claims 1-49 are pending. Claims 20-49 are withdrawn from consideration as being drawn to non-elected subject matter. Claims 1-19 have been considered in this Office Action.

Claim Objections

Claims 1-19 are objected to for the recitation of the acronym TFPI. The full name of the protein, tissue factor pathway inhibitor, should be provided in each independent claim. The acronym can be used after the first recitation of the full name followed by its acronym in parenthesis (tissue factor pathway inhibitor (TFPI)) in the independent claim and any which depends therefrom. Correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-17 are rejected under 35 U.S.C. 102(a) and 35 U.S.C. 102(e) as being anticipated by US 6,525,102 (the '102 patent).

The '102 patent issue date is February 25, 2003 which is before the earliest priority date of the present application (60/494,546, 8/13/03) and thus is considered anticipated under 35 U.S.C. 102(a). The '102 patent has a filing date of October 3, 2000 and thus is also considered anticipated under 35 U.S.C. 102(e).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art

under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The '102 patent teaches a purified preparation and pharmaceutical compositions comprising a plurality of tissue factor pathway inhibitor (TFPI) molecules. Absent evidence to the contrary, it appears that the preparation is patentably indistinguishable from that of the present claims. The '102 patent teaches that adding arginine, lysine, aspartic acid, or glutamic acid to a TFPI polypeptide composition protects TFPI from aggregation (Col. 6, lines 8-55). Thus, it appears that the TFPI preparation of the '102 patent has less than the claimed percent of aggregated TFPI. The '102 patent also teaches that the amino acids have inhibitory effects on deamidation of TFPI (Col. 7, lines 20-47). Thus, it appears that the TFPI preparation has less than the claimed percent of deamidated TFPI. The '102 patent teaches that methionine or EDTA can be added to the TFPI composition to protect the polypeptide against oxidation (Col. 10, lines 21-43). There is also no evidence or indication that the preparation of the '102 patent contains TFPI polypeptides that have cysteine adducts or are carbamylated. The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior

art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Claims 1-17 are rejected under 35 U.S.C. 102(b) as being anticipated by US 6,319,896 (the '896 patent, cited in IDS filed 1/10/05) .

The '904 publication teaches a purified preparation and pharmaceutical compositions comprising a plurality of tissue factor pathway inhibitor (TFPI) molecules. Absent evidence to the contrary, it appears that the preparation is patentably indistinguishable from that of the present claims. The '904 publication teaches that arginine is added to the TFPI polypeptide composition taught therein . Arginine protects TFPI from aggregation and misfolding (p. 16). Thus, it appears that the TFPI preparation of the '102 patent has less than the claimed percent of aggregated TFPI. There is also no evidence or indication that the preparation of the '904 publication contains TFPI polypeptides that have cysteine adducts or are carbamylated, oxidized, or deamidated. The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte

Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Claims 1-17 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 0 559 632 (the '632 publication).

The '632 publication teaches a purified preparation and pharmaceutical compositions comprising a plurality of tissue factor pathway inhibitor (TFPI) molecules. Absent evidence to the contrary, it appears that the preparation is patentably indistinguishable from that of the present claims. The '632 publication teaches that a TFPI preparation refolded and purified by the method disclosed therein was greater than 95% homogeneous suggesting that there was minimal misfolding, aggregation, carbamylation, oxidation, deamidation, or cysteine adducts. There is also no evidence or indication that the preparation of the '632 publication contains TFPI polypeptides that have cysteine adducts or are misfolded, aggregated, carbamylated, oxidized, or deamidated. The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989). Thus, absent

evidence to the contrary, it appears that the preparation of the '632 publication is patentably indistinguishable from that of the present claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,525,102 (the '102 patent) in view of EP 0 559 632 (the '632 publication).

The '102 patent teaches a purified preparation and pharmaceutical compositions comprising a plurality of tissue factor pathway inhibitor (TFPI) molecules. Absent evidence to the contrary, it appears that the preparation is patentably indistinguishable from that of the present claims. The '102 patent teaches that adding arginine, lysine, aspartic acid, or glutamic acid to a TFPI polypeptide composition protects TFPI from aggregation (Col. 6, lines 8-55). Thus, it appears that the TFPI preparation of the '102 patent has less than the claimed percent of aggregated TFPI. The '102 patent also teaches that the amino acids have inhibitory effects on deamidation of TFPI (Col. 7, lines 20-47). Thus, it appears that the TFPI preparation has less than the claimed percent of deamidated TFPI. The '102 patent teaches that methionine or EDTA can be added to the TFPI composition to protect the polypeptide against oxidation (Col. 10, lines 21-43). There is also no evidence or indication that the preparation of the '102

patent contains TFPI polypeptides that have cysteine adducts or are carbamylated. The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

The '102 patent teaches preparations of TFPI amino acid variants (Col. 17, lines 5-34) but does not specifically disclose Ala-TFPI. In addition, the preparations of the '102 patent include sodium citrate and L-arginine but the '102 patent only suggests that methionine can be added to prevent oxidation of the polypeptide.

The '632 publication teaches that constructs encoding Ala-TFPI improve expression of TFPI in E. coli (p. 8, lines 44-52).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the preparations of the '102 patent based on the teachings therein and in the '632 publication. More specifically, one of ordinary skill in the art would have been motivated to use Ala-TFPI since the '632 publication teaches that greater expression could be achieved with such a construct. In addition, one would have been motivated to place TFPI preparation in a formulation containing sodium citrate, L-arginine, and methionine since the '102 patent teaches that the higher the

concentration of L-arginine the greater the stability (and less aggregation) of the TFPI (Ex. 8 and Table 18), and that methionine can be used to reduce oxidation (and also increase stability) (Col. 30-31). It was well within the art to determine the sodium citrate concentration that would buffer the acidity of L-arginine and lead to greater TFPI stability (a goal of the '102 patent). Thus, one would have been motivated to combine the teachings of the '102 patent and the '632 publication to optimize the amount and stability of TFPI after expression and purification.

References Cited but not relied upon:

WO 2005/019265 claims priority to the same provisional applications as the present Application and contains the same claims. The references cited in the IDS filed 1/10/05 are the same as those listed in the International Search report of the '265 publication. These references also teach TFPI preparations but the information contained therein was considered additive to those of the rejections above.

Conclusions

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Tuesday-Thursday from 10 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Holly Schnizer
February 19, 2006